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Depressive and anxiety disorders: Associated with losing or gaining weight over 2 years?



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ABSTRACT

This longitudinal study examines to what extent different depressive and anxiety disorders and clinical characteristics are associated with subsequent weight change, while controlling for baseline weight, sociodemographics, health status, psychotropic medication use and (un)healthy lifestyle factors. Data are from a sample of 2447 respondents aged 18–65 years of the Netherlands Study of Depression and Anxiety (NESDA). Baseline depressive disorders and anxiety disorders were determined with the Composite International Diagnostic Interview (CIDI). Weight at baseline and after 2 years was measured and analyzed as continuous change score (mean change in weight 1 kg) and in categories of significant weight loss (< 1 S.D. weight change equaling < 4 kg), weight maintenance and weight gain (> 1 S.D., > 6 kg). After full adjustment for covariates baseline comorbid anxiety and depressive disorder and baseline Major Depressive Disorder (MDD) were associated with significant 2-year weight gain. Both current and remitted MDD at baseline and a baseline dysthymia, but none of the anxiety disorders, were associated with significant weight loss. This longitudinal study confirms a U-curved link between depression and weight change over 2 years. Furthermore, a dose–response effect of depression severity on 2-year weight gain was found.

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1. Introduction

Recent evidence has linked mental disorders and obesity – two highly prevalent conditions – together. For instance, there is convincing evidence that depression is associated with obesity and vice versa (Atlantis and Baker, 2008; de Wit et al., 2010a, 2010b; Luppino et al., 2010), although associations with underweight have also been found (Seidell et al., 1999; Flegal et al., 2007). In line with this, de Wit et al. (2009) and Zhao et al. (2009) found a U-curved association between depression and Body Mass Index (BMI). Although it has been less studied, there is also evidence for an association between anxiety and obesity (Garipey et al., 2010). Both weight gain and loss are associated with elevated health risks (Must et al., 1999; Newman et al., 2001; Field et al., 2001; Adams et al., 2006). Although weight change can also be beneficial for physical health outcomes for instance when overweight or obese adults lose weight (Resnick et al., 2000; Moore et al., 2005), the evidence for improvement on psychological wellbeing is less convincing (Koster et al., 2010;

Jackson et al., 2014). Prospective studies in the adult population have found that baseline depression and anxiety symptoms predicted weight gain at follow-up (Forman-Hoffman et al., 2007; Brumpton et al., 2013) and some recent studies found evidence for a bi-directional association between depression and weight gain (Koster et al., 2010; Singh et al., 2014). Patients with depressive and anxiety disorders however, constitute a very heterogeneous population, it is important to identify specific clinical factors (e.g. severity, subtype, age of onset, chronicity) that are associated with weight change in order to identify those who are most at risk. Recent studies found evidence that especially persons with atypical features have an elevated risk of weight gain (Leviton et al., 2012; Lasserre et al., 2014), which underlines the importance of investigating clinical characteristics. To further unravel the interplay between mental disorders and such a U-curved association with weight change, further longitudinal studies are necessary.

There is evidence that unhealthy lifestyles such as smoking, alcohol consumption and being both socially and physically inactive in adults is associated with having a depressive or anxiety disorder as well as with abnormal Body Mass Index (BMI) (van Gool et al., 2003; Berlin, 2008; Strine et al., 2008; de Wit et al., 2010a, 2010b). Hence, people with mental disorders might change

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weight as a result of adopting an unhealthy lifestyle. Therefore lifestyle behaviors are considered to be potential mediators in the association between depression and anxiety disorders and obesity (Friedman and Brownell, 1995). Nevertheless there are few studies that consider the influence of such lifestyle factors when studying the association between weight change and mental disorders. Some recent cross-sectional and longitudinal studies suggest that depressive and anxiety symptoms are associated with weight independently from lifestyle factors (physical activity, smoking and alcohol consumption) suggesting that there is no or a limited influence of lifestyle factors (Zhao et al., 2009). Furthermore the use of psychotropic medications, often prescribed for depressive and anxiety disorders, might be an additional explanatory risk factor for weight change (Virk et al., 2004; Demyttenaere and Jaspers, 2008; Vieweg et al., 2008; Hasnain and Vieweg, 2013). Underlying shared biological abnormalities such as inflammation, leptin or HPA-axis dysregulations could further play a linking role between mental health and weight change (Bjorntorp, 2001; Bornstein et al., 2006; Pasco et al., 2008; Vreeburg et al., 2009; Milaneschi et al., 2012).

There are previous studies that have investigated the association between weight change and mental disorders in the adult population, however most studies included adolescents (Haukka et al., 2001; Blaine, 2008; Liem et al., 2008; Luppino et al., 2010). Few of the large-scale studies examining mental health and weight associations have used well-defined DSM-IV depressive and anxiety diagnoses. Neither has the combined effect of depressive and anxiety disorders or the influence of specific characteristics of depressive and anxiety disorders (severity, subtype, chronicity, age of onset) been examined in longitudinal associations with weight change.

Based on previous research we expect to find an association between depressive and anxiety disorders and weight gain (Atlantis and Baker, 2008; de Wit et al., 2010a, 2010b; Luppino et al., 2010; Garipey et al., 2010; Koster et al., 2010; Brumpton et al., 2013; Singh et al., 2014) and an association between depressive disorders and weight loss (de Wit et al., 2009; Zhao et al., 2009) over a 2-year period. When studying the association, the extent to which specific clinical characteristics (severity, subtype, chronicity, age of onset, and the use of psychotropic medication) determine the association with subsequent weight loss and gain will be examined and the role of sociodemographics as well as (un)healthy lifestyle factors will be taken into account.

2. Methods

2.1. Study sample

Baseline and 2-year follow up data for this study were retrieved from the Netherlands Study of Depression and Anxiety (NESDA), a longitudinal cohort study designed to examine the long-term course of depressive and anxiety disorders. The total sample at baseline consists of 2981 respondents aged 18–65 years, of whom 1979 (66.4%) were females and 97% had the Dutch nationality. At baseline, a total of 1701 (57.1%) subjects had a current (6-month recency) anxiety or depressive disorder, 627 (21.0%) subjects had a remitted (lifetime but not current) anxiety or depressive disorder and there were 652 (21.9%) controls without a lifetime depressive or anxiety disorder. Respondents were recruited from the general population, in general practices and in mental health organizations. Exclusion criteria of the study were 1) a primary clinical diagnosis of a psychiatric disorder not subject of NESDA, e.g. psychotic disorder, obsessive compulsive disorder, or severe addiction disorder and 2) not being fluent in Dutch language. A detailed description of the baseline and 2-year follow up data collection procedures and study design of NESDA has been reported elsewhere (Penninx et al., 2008; Lamers et al., 2012).

The NESDA study protocol was approved centrally by the Ethical Review Committee of the VU University Medical Center and by the local review boards of each participating center. All respondents gave written informed consent. Both baseline and 2-year follow up assessment included a 4-h interview and self-reported data on mental health diagnoses, weight and height measures, lifestyle factors and sociodemographics at a

clinical site. For our longitudinal analyses we could not include a total of 534 persons of the original sample because they either dropped out at the 2-year follow up measure (non-response = 12.9%; $N=385$), or had missing values on our main outcome variables ($N=149$). These non-responders were younger, less educated, from non-European origin and more often suffering from depression, especially comorbid depressive and anxiety disorder and higher symptom severity (Lamers et al., 2012).

2.2. Depressive and anxiety disorders and clinical characteristics

At baseline the DSM-IV Composite International Diagnostic interview (CIDI, WHO version 2.1) was used to measure depressive and anxiety disorders: Major Depressive Disorder (MDD), Dysthymia, Generalized Anxiety Disorder (GAD), Social phobia, Panic disorder and Agoraphobia. The CIDI has proven to be a reliable and valid instrument to assess depressive and anxiety disorders (Wittchen, 1994). All respondents were assessed by specially trained clinical research staff at a clinical site (Penninx et al., 2008; Lamers et al., 2012).

We used a 5-category indicator to classify depressive and anxiety disorder status: healthy controls, remitted depressive or anxiety disorder (lifetime but not present in past six months), depressive disorder only (in past six months), anxiety disorder only (in past six months) and comorbid depressive and anxiety disorder (in past six months). In order to examine the role of specific disorders we used a 3-category indicator for each type of assessed disorder: healthy controls, remitted disorder (in lifetime but not present in past six months) and current disorder (in past six months).

Additionally considered clinical characteristics were severity, subtype, age of onset and duration. Severity of depressive symptoms was measured using the 28-item Inventory of Depressive Symptomatology (IDS) to obtain a score between 0 and 84. We used continuous as well as categorized severity scores of the IDS: none (0–13), mild (14–25), moderate (26–38), severe (39–48) very severe (49–84) (Rush et al., 1996, 2003). Severity of anxiety was measured with the 21-item Beck Anxiety Inventory (BAI) (Beck et al., 1988). The presence of symptoms of atypical depression and melancholic depression were assessed with the IDS as done before (van Reedt Dortland et al., 2010). Atypical depression is characterized by mood reactivity and at least 2 symptoms of vegetative reversal (including overeating, oversleeping, severe fatigue or leaden paralysis, and a history of rejection sensitivity) (Stewart and Thase, 2007). Melancholic depression is characterized by lack of mood reactivity or loss of pleasure and at least 3 symptoms of distinct mood quality (including mood worse in the morning, early morning awakening, psychomotor retardation or agitation, anorexia/weight loss and guilt feelings) (Kahn et al., 2008). Age of onset of the disorder was assessed with the CIDI interview. The Life Chart interview (Lyketos et al., 1994) was used to determine chronicity of the disorders in terms of the percentage of time in the 4 years prior to baseline that respondents had depressive and/or anxiety symptoms. Psychotropic medication use was based on drug container inspection of drugs used in the past month, and classified according to the WHO ATC classification.

Antidepressants were categorized as selective serotonin reuptake inhibitors (SSRIs) (ATC code N06AB), tricyclic antidepressants (TCAs) (ATC code N06AA), and other antidepressants (ATC codes N06AF and N06AX), anti-anxiety medication was categorized as Benzodiazepine use (no use/ infrequent use/ frequent use) (ACT code N05BA).

2.3. Weight assessment

At baseline and 2-year follow up, weight and height were measured by trained clinical research staff at a clinical site (Penninx et al., 2008; Lamers et al., 2012). Because psychopathology is associated with both high and low BMI the possibility exists of a U-shaped association between psychopathology and weight change (de Wit et al., 2009). Therefore we used a three category indicator for weight change (weight loss, weight maintenance and weight gain). Respondents were categorized by either clinically significant weight gain or weight loss when they changed at least 1 standard deviation ($S.D.=5$ kg) weight between baseline and follow up measure, calculated from the mean weight change (Mean = 1 kg weight gain) of the total sample (Newman et al., 2001; Stevens et al., 2006). We conducted additional analyses using a continuous indicator of weight change by calculating 2-year follow up weight minus baseline weight in order to obtain further confirmation of specific findings. A positive score indicates total kilograms weight gain and a negative score indicates total kilograms weight loss of a person.

2.4. Covariates

Baseline covariates included gender, age (continuous), years of education (continuous) and baseline height and weight. Baseline health status was measured by number of chronic diseases for which one receives medical treatment including lung disease, osteoarthritis, cancer, gastrointestinal disease, liver disease, epilepsy, thyroid disease. Lifestyle indicators included smoking status (never, current, former), alcohol intake (amount of alcoholic drinks a day), physical activity (continuous) and social activity (continuous). Physical activity was measured with the International Physical Activity Questionnaire (IPAQ), which has proven to be a valid and reliable instrument to measure physical activity (Craig et al., 2003;

Hagstromer et al., 2006). The overall energy expenditure was expressed in Metabolic Equivalent Total (MET)-units by calculating activity x frequency of the activity x MET intensity (Ainsworth et al., 1993; Craig et al., 2003). The total MET-minutes per week/1000 were used as a continuous indicator for physical activity. Furthermore we controlled for social activity because previous research has found social activity to be related to both weight and psychopathology (de Wit et al., 2010a, 2010b). Social activity was assessed by self-report. A continuous indicator was calculated by the frequency respondents visited a total of four social activities, 1) cultural events (theater, cinema, museum); 2) trips to nature or amusement parks or interesting buildings; 3) visiting a bar, restaurant or dancing; 4) attending an activity or meeting at a club or association.

2.5. Statistical analyses

Statistical analyses were conducted using SPSS 14.0 (Inc., Chicago, Illinois, USA). We described sociodemographics, lifestyle, antidepressant use and weight measures across depressive and anxiety status using χ^2 and ANOVA analyses. Multinomial regression analyses were adjusted in two steps 1) for sociodemographics, baseline height and weight (Forman-Hoffman et al., 2007; Koster et al., 2010; Lasserre et al., 2014) and 2) additionally for baseline health, psychotropic medication use and lifestyle indicators to examine the association between psychiatric status and weight change categories (weight loss and weight gain, with weight maintenance as reference). Adjusted linear regression analyses were conducted to examine the association between psychopathology and continuous 2-year weight change to confirm specific findings based on the categorical weight indicators. For both multinomial regression and linear regression analyses two separate models were tested. The first model examined the association with a 5-category indicator of depressive and anxiety status (healthy controls, remitted depressive and/or anxiety status, current depressive disorder only, current anxiety disorder only and current comorbid depressive and anxiety disorder). The second model examined simultaneously the association with individual DSM-IV depressive and anxiety disorders: MDD, Dysthymia, GAD, Social phobia, Panic disorder and Agoraphobia, specifying each specific disorder into: no disorder, remitted disorder or current disorder. We tested the interaction between sex and depression and anxiety status and weight loss and gain using multinomial logistic regression analysis, which appeared to be non-significant ($p=0.956$ and $p=0.825$ respectively).

In the subsample of respondents with a current depressive and/or anxiety disorder at baseline multinomial logistic regression analyses adjusted for covariates were used to examine the separate associations between weight change and clinical characteristics (severity, subtype, chronicity, age of onset and use of antidepressant medication). Subsequently, to test the independent association of clinical characteristics with weight change, one final multinomial regression analysis adjusted for covariates was conducted to test all clinical characteristics simultaneously.

3. Results

At baseline, 321 (13.0%) of the 2447 respondents had a current depressive disorder only, 447 (18.3%) a current anxiety disorder only, 562 (22.9%) a comorbid depressive and anxiety disorder, 548 (22.4%) had a remitted depressive and/or anxiety disorder and 569 (23.3%) were healthy controls. The mean age of the respondents included in these analyses was 42.3 years (S.D.=13.1) at baseline and 65.7% were female.

Between baseline and 2-year follow up the mean weight change of the total sample was +1 kg weight gain, with a standard deviation of 5 kg. We categorized 317 (13.0%) persons as weight gainers (≥ 6 kg) and 257 (10.5%) persons as weight losers (≥ 4 kg). Those persons who changed weight were more often persons with psychopathology ($p<0.001$). Furthermore respondents with current and remitted depressive and/or anxiety disorders in this sample were more often female, older, lower educated, socially inactive and were more likely to be a smoker (Table 1).

3.1. Psychopathology and weight change

Adjusted multinomial regression analyses were conducted to examine whether depressive and anxiety disorders at baseline were associated with both weight loss and weight gain (weight maintenance as reference) at 2-year follow-up while controlling for baseline height and weight, sex, age and years of education in the first step and additionally controlling for alcohol use, smoking, antidepressant use, benzodiazepine use, number of chronic

diseases, social activity and physical activity in the second step (Table 2). We did not find any significant associations between mental disorder status (at baseline) and weight loss. Having current MDD (OR=1.48; 95% CI: 1.00–2.20), a remitted MDD (OR=1.53; 95% CI: 1.05–2.24) or current dysthymia (OR=1.85; 95% CI: 1.14–3.00) were significantly associated with weight loss after adjusting for all covariates (step 2). Examining the continuous indicator for weight loss and the association with mental disorders gave similar results: persons with current dysthymia ($\beta=-0.07$; $p<0.001$) showed significantly more weight loss over a 2-year period.

Having a current comorbid depressive and anxiety disorder at baseline was significantly associated with weight gain (OR=2.06; 95% CI: 1.45–2.92), also after further adjustment for all covariates (OR=1.70; 95% CI: 1.16–2.50). Examining specific depressive or anxiety diagnoses at baseline, we found that weight gain was significantly associated with having current MDD (OR=1.66; 95% CI: 1.30–2.46). Furthermore, agoraphobia had elevated odds for weight gain after full adjustment as well, however this was not significant (OR=1.32; 95% CI: 0.80–2.18). Examining the continuous indicator for weight gain and mental disorders gave similar results: persons with comorbid depressive and anxiety disorder ($\beta=0.10$; $p<0.001$) and current MDD ($\beta=0.09$; $p<0.05$) and current panic disorder ($\beta=0.05$; $p<0.05$) showed more weight gain over a 2-year period.

3.2. Weight change and specific characteristics of psychopathology

To test whether specific clinical characteristics were associated with weight change we conducted multinomial regression analyses in the 1330 persons with a current depressive and/or anxiety disorder. Adjusted analyses per specific clinical characteristic are presented in Table 3. Weight loss was not associated with severity of anxiety, atypical and melancholic features, antidepressant medications, benzodiazepine use, and chronicity of symptoms or with age of onset. Severity of depression and severity of anxiety were found to be significantly associated with weight gain (OR per score increase=1.04; 95% CI: 1.03–1.06 and OR=1.03; 95% CI: 1.02–1.05 respectively). Also more melancholic features (OR=2.24; 95% CI: 1.43–3.52), more atypical features (OR=1.50; 95% CI: 1.02–2.21), using benzodiazepine (infrequent use: OR=1.85, 95% CI: 1.17–2.92, frequent use: OR=2.06, 95% CI: 1.23–3.27), and using SSRIs (OR=1.57; 95% CI: 1.11–2.23) were associated with weight gain.

Finally all clinical characteristics were examined in one multivariable model simultaneously which in order to examine independent effects. Severity of depression was the only clinical characteristic that remained a significant predictor for weight gain (OR per score increase=1.05; 95% CI: 1.02–1.07). Benzodiazepine use had elevated odds for weight gain as well, however this was not significant (infrequent use: OR=1.58; 95% CI: 0.98–2.56; frequent use: OR=1.53, 95% CI: 0.93–2.52). Fig. 1 shows the division of the relative weight change (RWC=(baseline weight-follow up weight)/baseline weight) categories across severity of depressive symptom categories. In line with our previous analyses we categorized a person with either weight loss or weight gain when the relative weight change was at least 1 standard deviation from the mean.

4. Discussion

Results of this longitudinal study showed that persons with a current comorbid depressive and anxiety disorder and a current MDD at baseline are more likely to experience significant weight gain over a 2-year period. Persons having a current MDD, a remitted MDD or current dysthymia at baseline more often

Table 1Description of baseline characteristics and weight (change) across depression and anxiety status groups (N=2447)^a.

	Value	N	%	Controls (N=569)	Remitted (N=548)	Depression only (N=321)	Anxiety only (N=447)	Comorbid anxiety and depression (N=562)	P
Demographics									
Gender	Female	1608	65.7	59.4	71.4	63.2	67.1	66.9	< 0.001
	Male	839	34.3	40.6	28.6	36.7	32.9	33.1	
Age(years)	Mean (S.D.)	42.3(13.1)		41.2(14.6)	44.6(13.0)	41.3(12.4)	41.9(12.6)	42.0(12.1)	< 0.001
Level of education	High	903	36.9	45.5	42.5	37.4	33.1	25.4	< 0.001
	Intermediate	1401	57.3	51.0	51.8	57.6	61.1	65.7	
	Low	143	5.8	3.5	5.7	5.0	5.8	8.9	
Health status	Mean(S.D.)	0.6(0.9)		0.5(0.8)	0.6(0.8)	0.6(0.9)	0.7(0.9)	0.6(0.9)	0.093
IDS	Mean(S.D.)	20.5(13.8)		8.3(7.2)	13.8(8.6)	27.1(11.0)	22.0(9.8)	34.4(11.9)	< 0.001
BAI	Mean(S.D.)	11.4(10.1)		3.9(4.7)	7.0(6.3)	11.4(7.9)	14.7(9.3)	20.4(10.6)	< 0.001
Age of Onset(year)	Mean(S.D.)	22.7(12.9)		32.2(12.6)	26.1(13.0)	26.0(13.1)	19.7(11.8)	19.7(12.1)	< 0.001
Duration of symptoms(months)	Mean(S.D.)	34.4(36.4)		6.9(17.7)	18.4(27.3)	36.5(29.6)	54.9(38.7)	60.7(33.8)	< 0.001
Benzodiazepine use	No	2087	85.3	97.4	91.2	84.4	81.9	70.5	< 0.001
	Unfrequent	193	7.9	2.3	6.6	7.2	10.7	13.0	
	Frequent	167	6.8	0.4	2.2	8.4	7.4	6.8	
Antidepressant use	No	1840	75.5	99.1	86.4	64.2	70.9	50.8	< 0.001
	SSRI	402	16.5	0.7	10.8	23.7	18.3	32.6	
	TCA	65	2.7	0.2	1.6	2.5	4.3	5.0	
	Other	130	5.4	0.0	1.1	9.5	6.5	11.6	
Daily alcohol use (unit's)	Mean(S.D.)	1.0 (1.4)		1.1(1.3)	1.0(1.3)	1.0(1.5)	1.0(1.5)	1.0(1.6)	0.853
Smoking status	No, never	713	29.1	37.6	26.6	26.8	23.4	29.0	< 0.001
	No, stopped	851	34.8	35.5	40.1	33.3	36.2	28.5	
	Yes, current	883	36.1	26.9	33.2	39.9	40.5	42.5	
Social activity	Mean (S.D.)	9.9(3.2)		10.8(2.9)	10.3(3.1)	9.6(3.2)	9.9(3.2)	8.7(3.0)	< 0.001
Physical activity (MET's)	Mean (S.D.)	3.7(3.1)		3.9(3.1)	3.9(2.9)	3.5(3.2)	3.7(3.0)	3.5(3.1)	0.185
Height	Mean(S.D.)	172.9(9.2)		173.9(9.5)	171.9(8.7)	173.7(9.2)	173.0(9.2)	172.9(9.2)	0.002
Weight measures(kg)									
Baseline weight	Mean(S.D.)	76.5(16.6)		75.8(16.1)	76.6(15.9)	77.4(17.4)	75.5(16.5)	77.5(17.5)	0.222
Follow up weight	Mean (S.D.)	77.4(16.6)		76.6(16.0)	77.0(15.9)	78.43(17.4)	76.3(16.6)	79.0(17.3)	0.042
Weight change^b	Loss	257	10.5	8.9	11.5	11.2	8.1	12.6	< 0.001
	Equal	1873	76.5	80.1	79.9	74.1	80.8	67.6	
	Gain	317	13.0	10.9	8.6	14.6	11.2	19.8	

^a Based on Pearson χ^2 and ANOVA analyses (unadjusted).^b Based on ≥ 1 S.D. (=5 kg) substantial weight change.

experienced weight loss. These associations were independent of sociodemographics, health status, and psychotropic medication use and (un) healthy lifestyle. These findings provide longitudinal confirmation of the earlier reported U-curved association between depressive disorders and weight change (Haukkala et al., 2001; de Wit et al., 2009). A dose–response association existed with more severe symptoms of depression being associated with more weight gain over a 2-year period.

This study showed that persons with a comorbid anxiety and depressive disorder had a 70% increased chance of gaining significant weight over a 2 year period. This was expected since persons with comorbid disorders have more severe symptoms (Lamers et al., 2011). In line with this, we found that depression severity was a predictor of weight gain. Increased appetite while experiencing stress is a feature of the atypical subtype. Contrary to previous studies we did not find an effect of atypical features on weight gain (Leviton et al., 2012; Lasserre et al., 2014). The observed effects in our study seemed mainly to be driven by overall severity of depression, but not very different for specific symptom profiles. (Angst et al., 2007; Lamers et al., 2010). In the present study we use the IDS for both subtype classification as well as severity classification, so it might as well be possible that subtype is overruled by severity. The high correlations between clinical characteristics in our study hinder to distinguish between the individual effects.

Furthermore we found evidence that persons with current MDD at baseline had a 66% increased chance of gaining 6 kg or more over a 2-year period compared to healthy controls. Persons

with current agoraphobia had a 32% increased chance of gaining 6 kg or more, however this result was not significant. However this might be due to the lack of power since only 152 (6.2%) persons in our study had a current agoraphobia at baseline. These findings support the results of recent meta-analyses that depressive and anxiety disorders at baseline lead to obesity at follow-up (Blaine, 2008; Gariepy et al., 2010; Luppino et al., 2010). Such a consequence could ultimately also contribute to the observed increased mortality and morbidity (e.g. cardiovascular disease and diabetes) among persons with depressive and anxiety disorders (Cuijpers and Smit, 2002; Nicholson et al., 2006; van Dooren et al., 2013). It has been hypothesized that depression and anxiety lead to weight gain through the adoption of unhealthy lifestyles in people with mental disorders such as increased food intake, smoking, alcohol consumption and decreased activity (Blaine, 2008; Faith et al., 2002; Kontinen et al., 2010). However in our study we found evidence for an association between mental disorders and weight gain independent of smoking, alcohol consumption, physical activity and social activity, which was in line with recent prospective studies that adjusted for lifestyle (Brumpton et al., 2013; Singh et al., 2014; Lasserre et al., 2014). The use of psychotropic medication has been suggested as a confounding factor in the association between psychopathology and weight change since medication use has shown to interact with mechanisms regulating food intake and appetite (Virk et al., 2004; Demyttenaere and Jaspers, 2008; Papakostas, 2008; Vieweg et al., 2008; Hasnain and Vieweg, 2013). Initially we found in a subsample of our study with persons having a current depressive and anxiety disorders that

Table 2Multivariate association between depressive and anxiety disorders and weight change ($N=2447$)^a.

		N	%	Weight loss adjusted ^a			Weight loss fully adjusted ^b			Weight gain adjusted ^a			Weight gain fully adjusted ^b		
				OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Model 1: Mental disorders in general															
Controls		569	23.3	ref			ref			ref			ref		
Remitted disorder		548	22.4	1.20	0.80–1.81	0.372	1.23	0.81–1.87	0.331	0.85	0.56–1.27	0.434	0.83	0.55–1.25	0.366
Current depressive disorder		321	13.1	1.22	0.76–1.96	0.408	1.32	0.81–2.18	0.268	1.41	0.93–2.14	0.105	1.21	0.78–1.87	0.387
Current anxiety disorder		447	18.3	0.84	0.53–1.34	0.475	0.93	0.56–1.51	0.778	1.02	0.68–1.52	0.936	0.90	0.60–1.37	0.633
Current comorbid disorder		569	23.0	1.43	0.96–2.14	0.082	1.45	0.92–2.29	0.110	2.06	1.45–2.92	< 0.001	1.70	1.16–2.50	0.007
Model 2: Specific disorders															
Major Depressive Disorder															
No		905	37.1	ref			ref			ref			ref		
Remitted		687	28.2	1.54	1.06–2.23	0.023	1.53	1.05–2.24	0.027	1.15	0.80–1.64	0.458	1.11	0.78–1.65	0.557
Current		845	34.7	1.41	0.97–2.06	0.070	1.48	1.00–2.20	0.051	1.81	1.31–2.48	< 0.001	1.66	1.30–2.46	0.002
Dysthemia															
No		1923	78.9	ref			ref			ref			ref		
Remitted		302	12.4	1.03	0.66–1.60	0.914	1.05	0.67–1.65	0.830	1.17	0.78–1.76	0.446	1.12	0.75–1.70	0.566
Current		212	8.7	2.02	1.28–3.19	< 0.001	1.85	1.14–3.00	0.012	1.46	0.96–2.22	0.078	1.33	0.86–2.21	0.197
Generalized Anxiety Disorder															
No		1827	75.0	ref			ref			ref			ref		
Remitted		271	11.1	0.91	0.58–1.42	0.669	0.90	0.57–1.43	0.664	0.73	0.47–1.15	0.178	0.77	0.49–1.21	0.258
Current		339	13.9	0.93	0.61–1.43	0.750	0.94	0.60–1.47	0.782	1.00	0.70–1.43	0.997	0.99	0.69–1.42	0.958
Social Phobia															
No		1717	70.5	ref			ref			ref			ref		
Remitted		203	8.3	0.83	0.49–1.40	0.487	0.89	0.52–1.51	0.661	0.79	0.48–1.31	0.364	0.82	0.49–1.37	0.450
Current		517	21.2	1.03	0.72–1.47	0.871	1.06	0.73–1.53	0.775	0.80	0.58–1.10	0.162	0.78	0.57–1.08	0.135
Panic disorder															
No		1753	71.9	ref			ref			ref			ref		
Remitted		179	7.3	0.82	0.48–1.39	0.458	0.86	0.50–1.47	0.576	0.62	0.35–1.13	0.123	0.63	0.33–1.09	0.095
Current		505	20.7	0.80	0.54–1.17	0.246	0.84	0.56–1.26	0.391	1.42	1.04–1.94	0.027	1.31	0.95–1.81	0.094
Agoraphobia															
No		2201	90.3	ref			ref			ref			ref		
Remitted		84	3.4	1.14	0.57–2.28	0.722	1.10	0.54–2.26	0.793	1.19	0.59–2.41	0.633	1.19	0.58–2.42	0.633
Current		152	6.2	1.01	0.58–1.77	0.970	1.04	0.58–1.86	0.892	1.40	0.86–2.30	0.179	1.32	0.80–2.18	0.274

^aAnalyses adjusted for psychopathology, baseline weight, baseline height, sex, age, years of education, alcohol use, smoking, antidepressant use, benzodiazepine use, number of chronic diseases, social activity and physical activity.

^a Based on adjusted multinomial logistic regression analyses. Categories based on ≥ 1 S.D. (=5.0 kg) substantial weight change and weight maintenance as reference category.

^b Analyses adjusted for baseline weight, baseline height, sex, age and years of education.

Table 3Multivariate associations between characteristics of mental disorders and weight change in the subsample of persons with a current depressive or anxiety disorder ($N=1330$)^{a,b}.

Characteristics of mental disorders	Weight loss ^a			Weight loss ^b			Weight gain ^a			Weight gain ^b		
	OR	95%CI	P	OR	95%CI	P	OR	95%CI	P	OR	95%CI	P
Depression severity	1.02	1.00–1.03	0.117	1.02	0.99–1.05	0.133	1.04	1.03–1.06	< 0.001	1.05	1.02–1.07	< 0.001
Severity of melancholic features	0.90	0.546–1.76	0.762	0.60	0.28–1.31	0.199	2.24	1.43–3.51	< 0.001	1.00	0.58–1.71	0.996
Severity of atypical features	1.54	0.98–2.43	0.06	1.23	0.72–2.12	0.453	1.50	1.02–2.21	0.040	0.79	0.50–1.24	0.302
Anxiety severity	1.01	0.99–1.02	0.604	0.99	0.97–1.02	0.478	1.03	1.02–1.05	< 0.001	1.00	0.98–1.02	0.952
Chronicity of symptoms	1.00	1.00–1.01	0.382	1.00	1.00–1.01	0.460	1.00	1.00–1.01	0.834	1.00	0.99–1.00	0.259
Age of onset	1.00	0.99–1.02	0.760	1.01	0.99–1.02	0.567	1.00	1.00–1.00	0.565	1.01	0.99–1.02	0.476
Antidepressant use none	ref			ref			ref			ref		
SSRI	0.85	0.55–1.39	0.574	0.88	0.54–1.44	0.606	1.57	1.11–2.23	0.010	1.20	0.82–1.74	0.349
TCA	1.44	0.64–3.23	0.371	1.39	0.60–3.21	0.437	0.90	0.36–2.25	0.824	0.75	0.30–1.95	0.564
Other	0.88	0.42–1.68	0.637	0.88	0.43–1.76	0.708	1.60	0.96–2.68	0.073	1.21	0.70–2.10	0.487
Benzodiazepine use												
No	ref			ref			ref			ref		
Unfrequent	0.99	0.54–1.83	0.984	1.09	0.59–2.03	0.776	1.85	1.17–2.92	0.008	1.58	0.98–2.56	0.063
Frequent	0.87	0.48–1.61	0.665	0.77	0.40–1.50	0.447	2.06	1.23–3.27	0.002	1.53	0.93–2.52	0.098

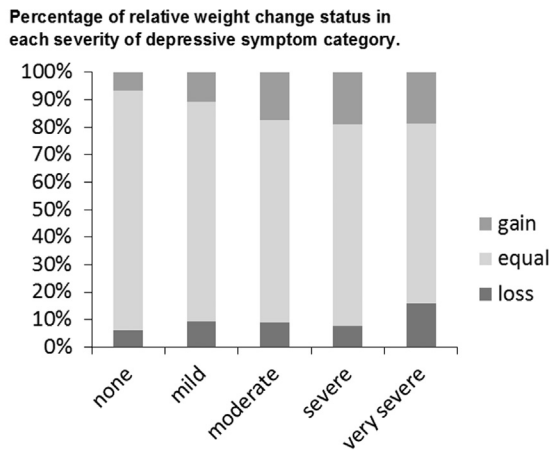
Based on ≥ 1 S.D. (=5.0 kg) substantial weight change.

^a Based on multinomial logistic regression analyses, baseline height, weight, sex, age, years of education smoking status, alcohol use, social activity, physical activity and number of chronic diseases.

^b Based on multinomial logistic regression analyses, baseline height, weight, sex, age, years of education, smoking status, alcohol use, social activity, physical activity, number of chronic diseases and all other characteristics of mental disorders.

SSRI users as well as benzodiazepine users compared to non-users were more likely to gain weight. However, the found effects for SSRI use seemed to be mainly driven by the severity of the depressive symptoms. Surprisingly, the effect of benzodiazepine use on weight gain remained borderline significant after full adjustment, which is conflicting with previous research which found that benzodiazepine use was weight neutral (Vieweg et al.,

2008; Hasnain and Vieweg, 2013). Other explaining mechanisms for the association between mental disorders and subsequent weight increase are physiological abnormalities found in depressed persons such as increased inflammation, and long-term disturbances of the HPA-axis. These abnormalities also form risk factors for obesity (Bjorntorp, 2001; Bornstein et al., 2006; Vreeburg et al., 2009). Further research is needed to examine the



Note: Relative weight change was calculated by (baseline weight-follow up weight)/baseline weight.
A person with either weight loss or weight gain when the relative weight change was at least 1 standard deviation from the mean.

Fig. 1. Percentage of relative weight change status in each severity of depressive symptom category.

influencing role of pathophysiological factors in the link between mental disorders and weight change.

Persons with a current MDD, as well as persons with current dysthymia were more likely to lose 4 kg's or more over a 2-year period independent of lifestyle and health status. These findings confirm our hypothesis of a U-shaped association between weight change and depressive disorders (Forman-Hoffman et al., 2007; de Wit et al., 2009; Zhao et al., 2009). Nevertheless, further studies are needed to confirm the association between MDD and dysthymia and weight loss.

Increased and decreased appetite are core features of depression diagnosis which is an explanatory factor of weight change in depressed persons (Privitera et al., 2013). In addition, previous research reported an association between food insufficiency and dysthymia, however this was not found for MDD (Alaimo et al., 2002). Further research should examine the mediating influence of eating behaviors on the association between anxiety and depressive disorders and weight change (Torres and Nowson, 2007).

Persons with remitted MDD had a 53% increased chance of losing > 4 kg over a 2-year period. It is likely that the persons who gain weight when having a current MDD episode may be the same persons who also lose weight when the MDD is remitted because of a healthier lifestyle or restored biological dysfunction. In addition to this it must be noted that weight change is not an indicator of psychological distress in all cases (Forman-Hoffman et al., 2007; Koster et al., 2010; Jackson et al., 2014). In some cases it can even be an indicator of well-being. For instance both persons who were underweight before and gain weight and persons who were overweight and lose weight, weight change is likely to have positive effect on well-being (Resnick et al., 2000; Moore et al., 2005).

Consequently, this might suggest that MDD patients when in remission lose some of the weight that they gained when symptomatic. The mechanisms that cause weight loss in remitted depressed persons, e.g. healthier food intake or restored biological dysfunction, require more longitudinal research. The observed U-curved association between depression severity and weight change suggests that there are diverse mechanisms underlying the association between depression and unhealthy weight, one pathway leading to weight gain and one leading to weight loss.

A limitation of this study was the relatively short follow-up period of two years. Previous research has demonstrated stronger associations between obesity and depression after a follow-up period of 10 years (Luppino et al., 2010). It must be noted that age of onset is based on retrospective reports which have a risk of an incorrect recall (Simon and VonKorff, 1995; Kessler et al., 2007). Furthermore,

previous studies provided evidence for a bi-directional association between mental disorders and weight change (Koster et al., 2010; Singh et al., 2014). However, in our study we were not able to investigate the effect of weight change on the onset of depressive and anxiety disorders since data on weight status previous to baseline measures were not available. An additional limitation is the lack of eating behaviour information which did not allow us to examine underlying nutritional variations as explaining mechanisms in the observed associations. When examining specific disorders we adjusted for comorbidity and therefore were not able to look at the joint effects of specific disorders. Future research has to focus on the effect of comorbid depressive and anxiety diagnoses on weight gain. There was a drop out of 12.9% at the 2 years follow up assessment. However these persons suffered from more severe symptoms we do not expect this to affect the results (Lamers et al., 2012).

The strength of this study is the use of a large study sample and detailed assessment in which we were able to separate and compare the impact of DSM-IV based depressive and anxiety diagnoses on weight change. Weight and height were measured by well-trained research staffs which limit the possibility of bias that often occurs with self-report (Gorber et al., 2007). Furthermore we were able to examine specific characteristics of depressive and anxiety disorders and examine the role of various sociodemographic and lifestyle factors.

In sum, this study gives longitudinal evidence for a U-shaped association between depressive disorders and weight change independent of lifestyle, health status, psychotropic medication use and socio-demographic factors. A depressive disorder is a possible risk factor for gaining weight as well as losing weight, which are both linked to increased mortality. These two different pathways suggest that diverse mechanisms can be activated in depressed persons, one leading to weight gain and another leading to weight loss. Future research should focus on exploring which differential mechanisms underlie these diverse patterns. Our results imply that it is important for clinicians to monitor the weight changes when a person is suffering from depression in order to prevent an unhealthy weight.

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